1: Mol Carcinog. 2000 Oct;29(2):112-26.

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Enhanced tumorigenesis and reduced transforming growth factor-beta type II receptor in lung tumors from mice with reduced gene dosage of transforming growth factor-beta1.

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To elucidate the role of transforming growth factor-beta1 (TGF-beta1) and the TGF-beta type II receptor (TGF-beta RII) as tumor-suppressor genes in lung carcinogenesis, we mated C57BL/6 mice heterozygous (HT) for deletion of the TGF-beta1 gene with A/J mice to produce AJBL6 TGF-beta1 HT progeny and their wild-type (WT) littermates. Immunohistochemical staining, in situ hybridization, and northern blot analyses showed lower staining and hybridization for TGF-beta1 protein and mRNA, respectively, in the lungs of normal HT mice versus WT mice. Competitive reverse transcription-polymerase chain reaction (CRT-PCR) amplification showed the level of TGF-beta1 mRNA in the lungs of HT mice to be fourfold lower than the level in WT lung. When challenged with ethyl carbamate, lung adenomas were detected in 55% of HT mice by 4 mo but only in 25% of WT littermates at this time. Whereas all HT mice had adenomas by 6 mo, it was not until 10 mo before all WT mice had adenomas. After 12 mo, the average number of adenomas was fivefold higher in HT lungs than in WT lungs. Most dramatic was the appearance of lung carcinomas in HT mice 8 mo before they were visible in WT mice. Thus, the AJBL6 TGF-beta1 HT mouse provides an excellent model system to examine carcinogen-induced lung tumorigenesis by increasing progressive lesion incidence and multiplicity relative to their WT littermates. Immunohistochemical staining showed expression of the TGF-beta type I receptor (TGF-beta RI) at moderate to strong levels in lung adenomas and carcinomas in HT and WT mice. In contrast, whereas weak immunostaining for TGF-beta RII was detected in 67% of HT carcinomas at 12 mo, only 22% of WT carcinomas showed weak staining for this protein. Individual lung carcinomas showing reduced TGF-beta RII expression and adjacent normal bronchioles were excised from HT lungs using laser capture microdissection, and CRT-PCR amplification of the extracted RNA showed 12-fold less TGF-beta RII mRNA in these carcinomas compared with bronchioles. Decreasing TGF-beta RII mRNA levels occurred with increasing tumorigenesis in lung hyperplasias, adenomas, and carcinomas, with carcinomas having fourfold and sevenfold lower levels of TGF-beta RII mRNA than adenomas and hyperplasias,

respectively. These data show enhanced ethyl carbamate-induced lung tumorigenesis in AJBL6 HT mice compared with WT mice, suggesting that both TGF-beta1 alleles are necessary for tumor-suppressor activity. Reduction of TGF-beta RII mRNA expression in progressive stages of lung tumorigenesis in HT mice suggests that loss of TGF-beta RII may play an important role in the promotion of lung carcinogenesis in mice with reduced TGF-beta1 gene dosage when challenged with carcinogen.

PMID: 11074608 [PubMed - indexed for MEDLINE]